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Predictors of False-Negative Results from Percutaneous Transthoracic Fine-Needle Aspiration Biopsy: An Observational Study from a Retrospective Cohort

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Purpose: We investigated factors predictive of false-negative pulmonary lesions with nonspecific benign cytology results on percutaneous transthoracic fine-needle aspiration biopsy (FNAB).

Materials and Methods: We included 222 pulmonary lesions that had a nonspecific benign result from percutaneous transthoracic FNAB between March 2005 and December 2012, and were confirmed by subsequent pathologic results or adequate clinical follow up over at least 2 years. Clinical, imaging, and biopsy procedure-related findings were compared between lesions with a final diagnosis of malignancy (false-negative) and lesions with a benign diagnosis (true-negative). Multivariate logistic regression analysis was performed to identify significant predictors of false-negatives.

Results: Of 222 lesions, 115 lesions were proved to be false-negatives, and 107 were true-negatives. Compared with the true-negatives, false-negative lesions showed significantly older age (p=0.037), higher maximum standardized uptake value (SUVmax) on positron emission tomography (p=0.001), larger lesion size (p=0.007), and lesion characteristics of a subsolid nodule (p=0.007). On multivariate logistic regression analysis, SUVmax, lesion size, and lesion characteristics were significant predictors of false-negative results.

Conclusion: Among the clinical, radiologic, and procedure-related factors analyzed, high SUVmax, large lesion size, and subsolid lesions were useful for predicting malignancy in pulmonary lesions with nonspecific benign cytology results on FNAB.

Key Words: Fine needle aspiration, lung cancer, positron-emission tomography

INTRODUCTION

With increasing use of screening computed tomography (CT) scans, more frequent detection of indeterminate pulmonary nodules creates a growing need for further clinical evaluation, including percutaneous transthoracic fine-needle aspiration biopsy (FNAB). Percutaneous transthoracic FNAB has a high diagnostic yield for malignancy.[1] However, the diagnostic yield of FNAB for benign lesions is lower (10–50%),[2-5] and widely variable false-negative rates (3.8–62.5%) have been reported using percutaneous transthoracic FNAB without rapid on site evaluation of cytopathology.[6-8] One of the major limitations of FNAB is that malignancies cannot be excluded without a specific benign diagnosis, even with a negative cytologic result. Although the incidence of positive results on repeated biopsies is up to 50% in those with suspected malignancy, the uncertainty must be resolved in cases of nonspecific negative results.[9] Patients with these FNAB results should undergo tissue resampling with biopsy or surgical resection, or close clinical and imaging follow up. A few previous studies have investigated the false-negative rates of FNAB and factors related to false-nega-

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tive results.[6,8] However, those studies mostly included small population sizes and only a few parameters that predict false-negative lesions.

Therefore, the purpose of our study was to identify clinical, radiologic, and procedure-related factors that predict malignancy in pulmonary lesions with nonspecific benign cytology results on percutaneous transthoracic FNAB.

MATERIALS AND METHODS

Institutional Review Board approval was obtained, and informed consent was waived for this retrospective and observational study.

Patients

We included a retrospective cohort of patients who underwent percutaneous transthoracic FNAB at our institution from March 2005 to December 2012. Among 1726 pulmonary lesions that underwent percutaneous transthoracic FNAB, we included only lesions that showed initial "nonspecific benign" cytology and had adequate follow up (Fig. 1). The initial cytology results from FNAB were classified as positive for malignancy, atypical cell (significant but nondiagnostic atypia present), specific benign, negative for malignancy (nonspecific benign), or inadequate specimen (specimens that did not include pulmonary macrophages or bronchial lining cells).[10] Specific benign results were defined as a benign lesion (e.g., hamartoma and granuloma) or inflammatory cells with a positive bacterial, fungal, or mycobacterial culture that could explain the radiologic findings. Negative for malignancy was defined as the presence of benign cellular material (e.g., inflammatory cells), but not specific enough to render a diagnosis. Lesions with results of positive for malignancy (n=931), "presence of atypical cells" (n=63), specific benign (n=56), or inadequate specimen (n=312) were excluded from analysis. For adequate follow up, the biopsied lesion was either 1) followed for at least 2 years by CT demonstrating resolution or no growth; 2) showed complete resolution within 2 years of follow-up CT; 3) had a subsequent surgical biopsy or repeated biopsy of the pulmonary lesion (percutaneous transthoracic FNAB or core needle biopsy, or transbronchial lung biopsy); or 4) the patient underwent a biopsy from another body site. We excluded 134 lesions with nonspecific benign cytology results that did not receive adequate clinical follow up, and eight lesions because of no available CT image data. Five patients underwent FNAB twice for the same lesion. Finally, 222 lesions in 217 patients (129 males and 88 females) were included in the analysis.

FNAB technique

The FNAB procedures were performed by one of three experienced chest radiologists who had 5, 7, and 11 years of experience performing thoracic biopsies respectively. CT guidance was performed with a CT fluoroscopy technique using a 16-multidetector CT scanner (Somatom Sensation 16; Siemens Medical Solutions, Erlangen, Germany) equipped with CARE Vision software (Siemens Medical Solutions). The exposure parameters were 120 kV, 30 mAs, and slice thickness of 6 mm. Ultrasound (US) guidance was performed using a US system (HDI5000; ATL Philips, Bothell, VA, USA) equipped with a 3.5- to 5.0-MHz convex probe. The biopsy needle was inserted by a freehand out-of-plane approach and then advanced into the lesion with real-time visualization. Fluoroscopy-guidance was performed using a fluoroscope (Medix 130, Hitachi Med. Corp,

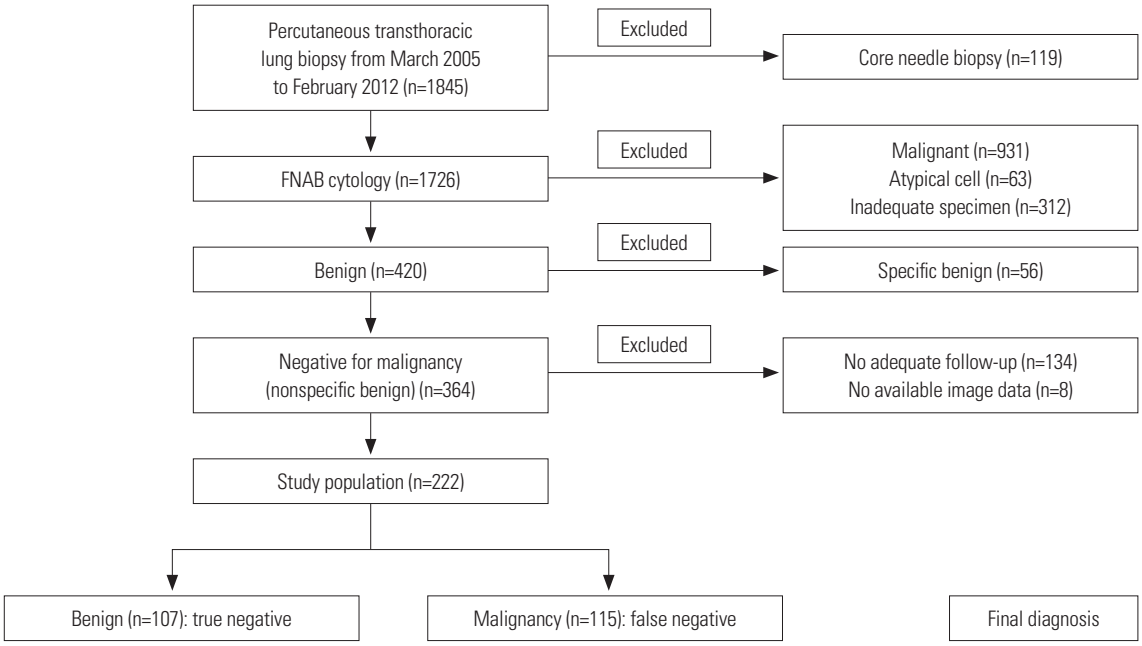

Fig. 1. Flow diagram of this study. FNAB, fine-needle aspiration biopsy.

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Tokyo, Japan). All procedures were performed with the patients in a prone, supine, or lateral decubitus position, depending on the location of the lesion. The puncture area was cleaned with antiseptic solution followed by administration of local anesthetic by subcutaneous injection of 1% lidocaine (Xylocaine, AstraZeneca, Wilmington, DE, USA). In all cases, at least two aspiration specimens were obtained using 20- to 22-gauge Chiba needles to obtain sufficient specimen. The specimen was placed in 99% ethyl alcohol for cytologic examination.

Data analysis

Final diagnosis was determined in review of pathologic results or follow-up imaging results. True-negative cases were defined as those demonstrating CT stability for at least 2 years, complete resolution of the lesion of interest on follow-up imaging, or those that underwent a surgical biopsy that demonstrated a benign process. False-negative cases were defined as those in which the diagnosis of malignancy was established by pathology from a subsequent surgical biopsy, repeated biopsy, or from biopsy results from another site of the body with an increase in size of the primary lung lesion on follow-up imaging.

Data regarding clinical variables were collected, including smoking status, number of pack years, history of prior malignancy, and serum tumor marker levels [carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA 21-1), and squamous cell carcinoma antigen (SCC Ag)]. An elevated serum tumor marker level was defined as at least one tumor marker with a level higher than the reference value (5.0 ng/mL for CEA, 3.3 ng/mL for CYFRA 21-1, 1.5 ng/mL for SCC Ag).[11,12]

CT images obtained at the time of biopsy or within less than 1 week of FNAB were retrospectively reviewed by two radiologists (with 2 and 11 years of experience in both reading CT scans and performing FNAB, respectively) who were blinded to the outcomes of the FNAB and who did not perform any of the FNAB procedures. Final decisions were made through consensus reading when there was a discrepancy between observers. The radiologic variables analyzed for each lesion included the size of the lesion, location of the lesion (upper, middle, or lower), and lesion characteristics [solid, subsolid, or consolidation in appearance; presence of necrosis (low-density area or poorly-enhancing area); cavitation within the lesion]. We also collected information on FNAB procedure-related variables that might affect the results, including the distance between the pleura, the type of imaging modality used for guidance, the number of aspirated samples, and whether there were complications at any point during or immediately after the procedure (e.g., pneumothorax or hemoptysis). When lesions had subsolid characteristics, whether the FNAB needle approached the solid portion or ground-glass portion was also assessed.

Recent (within 3 months of FNAB) positron emission tomography (PET) imaging data were also reviewed, if available, by an experienced reviewer (with 5 years of experience in nuclear medicine). All ^{18}F-fluorodeoxyglucose (FDG) PET/CT scans were obtained with a dedicated PET/CT scanner [Discovery Ste (GE Healthcare, Little Chalfont, Buckinghamshire, UK) or Biograph TruePoint 40 (Siemens Healthcare, Erlangen, Germany)]. ^{18}F-FDG PET/CT images were reviewed by one nuclear medicine physician using an Advantage Workstation 4.5 (GE Healthcare). Maximum standardized uptake value (SUVmax), mean SUV (SUVmean), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) on PET images were measured using volume viewer software. Each biopsied pulmonary lesion was examined with a spheric-shaped volume of interest (VOI) that included the entire lesion in the axial, sagittal, and coronal planes. SUVmax of the VOI was calculated as (decay-corrected activity/tissue volume)/(injected dose/body weight). MTV was defined as the total tumor volume with an SUV of 2.5 or greater, and the MTV and SUVmean of the VOI were automatically calculated. TLG was calculated as (SUVmean)×(MTV).[13]

For false-negative lesions, the pathology results of final diagnosis, the method used to confirm the final diagnosis, and staging at the time of FNAB were recorded to determine the impact of the delay in diagnosis.

Statistical analysis

False-negatives were compared with true-negatives in terms

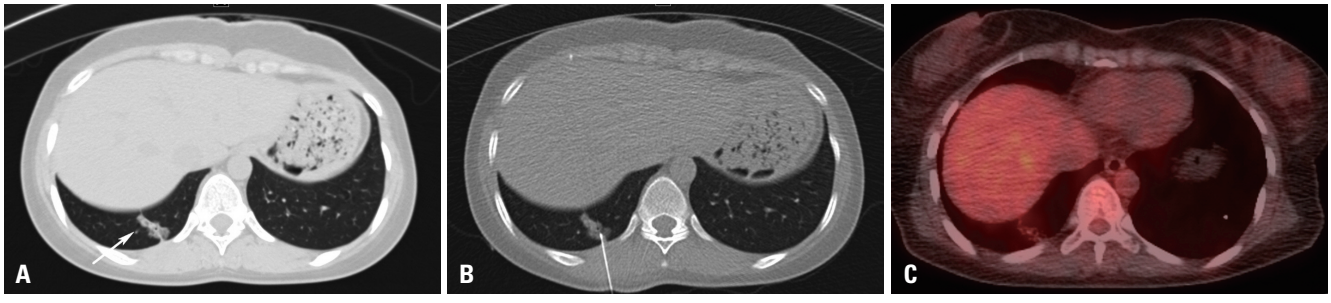

Fig. 2. CT and PET images of a false-negative case of a 45-year-old female. (A) CT image prior to FNAB shows a 2.4 cm subsolid nodule in the right lower lobe (arrow). (B) CT image obtained during FNAB shows the needle targeting the subsolid lesion. FNAB cytology result was negative for malignancy. (C) On PET image performed 16 days before FNAB, no increased FDG uptake is seen with the SUVmax measured to be 1.3. Final diagnosis after surgical resection was invasive adenocarcinoma. CT, computed tomography; PET, positron emission tomography; FNAB, fine-needle aspiration biopsy; FDG, fluorodeoxyglucose; SUVmax, maximum standardized uptake value.

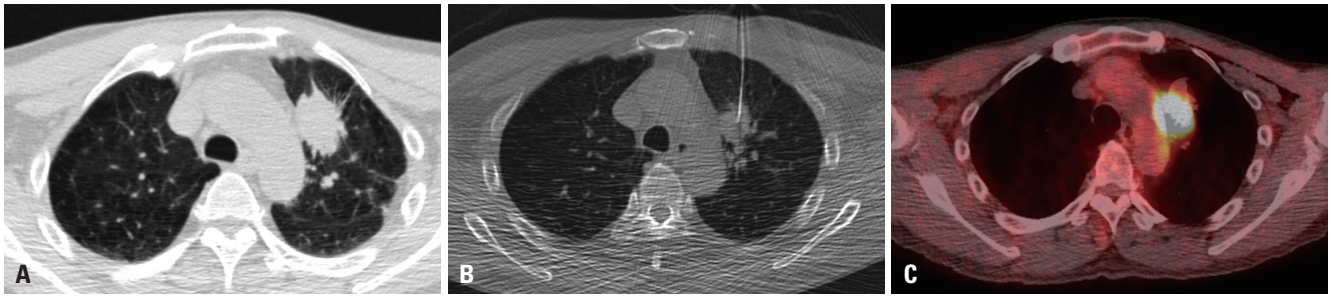

Fig. 3. CT and PET images of a false-negative case of a 64-year-old female. (A) CT image prior to FNAB shows a 3.7 cm solid mass in the left upper lobe. (B) CT image obtained during FNAB shows the needle targeting the solid nodule. FNAB cytology result was negative for malignancy. (C) On PET image performed 1 day after FNAB, increased FDG uptake is seen with the SUVmax measured to be 30.5. Final diagnosis after surgical resection was invasive adenocarcinoma. CT, computed tomography; PET, positron emission tomography; FNAB, fine-needle aspiration biopsy; FDG, fluorodeoxyglucose; SUVmax, maximum standardized uptake value.

Table 1. Comparison of Clinical, Radiologic, and Procedure-Related Characteristics between False-Negative and True-Negative Lesions

	True-negative (n=107)	False-negative (n=115)	*p* value
Clinical variables			
Age (yrs)	59.6±11.2	62.8±11.3	0.037
Male	63 (58.9)	67 (58.3)	0.966
Smoking			
Current smoker	7 (6.5)	7 (4.6)	0.893
Pack years	15.5±21.3	19.1±26.9	0.231
History of prior malignancy	31 (28.2)	32 (26.5)	0.968
Elevated serum tumor marker	16 (19.5) (n=82)	29 (30.2) (n=96)	0.143
Serum CEA level (n=174)	6.27±16.6 (n=80)	24.6±176 (n=94)	0.319
Serum CYFRA 21-1 level (n=117)	3.22±8.94 (n=49)	5.42±14.8 (n=68)	0.317
Serum SCC Ag level (n=50)	0.836±0.9 (n=22)	1.31±2.7 (n=28)	0.374
Radiologic variables			
PET parameters (n=132)			
SUVmax	4.4±3.8 (n=46)	7.2±5.5 (n=86)	0.001
MTV2.5 (mL)	10.7±23.6 (n=44)	34.7±68.4 (n=86)	0.004
TLG2.5	44.2±109.6 (n=44)	176.1±371.4 (n=86)	0.003
Size of lesion (mm)	20.9 (14.3–31.2)	25.6 (17.5–44.0)	0.007
Location			0.906
Upper	41 (47.7)	45 (52.3)	
Middle	14 (45.2)	17 (54.8)	
Lower	52 (49.5)	53 (50.5)	
Imaging characteristics			0.007
Solid nodule (n=191)	96 (50.3)	95 (49.7)	
Subsolid nodule (n=19)	3 (15.8)	16 (84.2)	
Consolidation (n=12)	8 (66.7)	4 (33.3)	
Presence of necrosis	32 (59.3)	22 (40.7)	0.087
Presence of cavitation	12 (42.9)	16 (57.1)	0.687
Procedure-related variables			
Distance from pleura to lesion (mm)	16.0±14.7	16.6±16.0	0.762
Types of imaging guidance			0.499
CT (n=149)	73 (49.0)	76 (51.0)	
Fluoroscopy (n=63)	31 (49.2)	32 (50.8)	
US (n=10)	3 (30.0)	7 (70.0)	
Number of FNAB samples	1.97±0.17	1.99±0.21	0.445
Complication	19 (17.8)	28 (24.3)	0.3

CEA, carcinoembryonic antigen; CYFRA 21-1, cytokeratin 19 fragment; SCC Ag, squamous cell carcinoma antigen; PET, positron emission tomography; SUVmax, maximum standardized uptake value; MTV, mean tumor volume; TLG, total lesion glycolysis; CT, computed tomography; US, ultrasound; FNAB, fine-needle aspiration biopsy.
Data are given as n (%) or mean±standard deviations.

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of clinical, radiologic, and procedure-related variables. For categorical variables, a chi-square test or Fisher's exact test was performed. For continuous variables, an independent Student's t-test or Mann-Whitney test was performed. For radiologic variables of CT images, interobserver variability was assessed using weighted-kappa statistics or intraclass correlation coefficients. Univariate and multivariate logistic regression analyses were performed to determine significant predictors of malignancy. Receiver operating characteristic (ROC) curves were calculated to determine the best cutoff values for lesion size and PET parameters for differentiating true-negative and false-negative lesions. Odds ratio (OR) and 95% confidence interval (CI) for differentiating true and false-negative lesions were calculated for each variable. Because PET imaging were not available for all included lesions, we constructed two models for multivariate logistic regression analysis (Model 1: PET parameter+other variables; Model 2: other variables except PET parameter) and compared the area under the ROC curve of each logistic regression analysis to identify significant predictors. A probability value <0.05 was considered significant. For statistical analysis we used SPSS software (version 18.0 for Microsoft Windows, SPSS Inc., Chicago, IL, USA).

RESULTS

Patient and lesion characteristics

Among 222 lesions, 115 (51.8%) were proven to be false-negatives and 107 (48.2%) were true-negatives at final diagnosis. Of the 115 false-negative lesions, final diagnosis was confirmed by subsequent surgery in 62 lesions, by repeated biopsy in 33 lesions, by biopsy of other sites in nine, and by follow-up CT imaging in 11 (mean follow-up period 458.1 days, range 89–1379 days). Among the 107 true-negative lesions, final diagnosis was confirmed by subsequent surgery in 27 lesions, by repeated biopsy in four, by biopsy of other sites in three, and by follow up in 73 (mean follow-up period, 1167 days, range 41–2628 days), respectively. Compared with true-negatives, false-negative lesions had a significantly older age (p=0.037), higher SUVmax, TLG, and MTV on PET (p<0.05), larger lesion size (median 25.6 mm vs. 20.9 mm, p=0.007), and a higher percentage of lesions with characteristics of subsolid lesions (p=0.007) (Figs. 2 and 3, Table 1). Among 19 subsolid lesions, four had no solid portion, and the FNAB needle approached the solid portion of all remaining lesions except one.

Interobserver variability for assessment of radiologic variables

The intraclass correlation coefficient for agreement between the two readers for lesion size was 0.946 (95% CI, 0.930–0.958), representing excellent agreement. Weighted kappa values for agreement for other radiologic variables were 0.834 (95% CI, 0.772–0.895) for lesion location, 0.720 (95% CI, 0.583–0.857),

Table 3. Clinical Findings of False-Negative Cases (n=115)

Final diagnosis	
Adenocarcinoma	52
Squamous cell carcinoma	16
Small cell carcinoma	10
Large cell carcinoma	3
Metastasis	16
Lymphoma	4
Adenosquamous cell carcinoma	1
Non-small cell carcinoma	7
Sarcomatoid	1
Undetermined	5
Method of confirmation of final diagnosis	
Surgery	62
Repeated biopsy (FNAB or TBLB)	33
Other site biopsy	9
Follow up	11
Interval to final diagnosis	Mean 105.1±221.9 days (range, 0–1379 days)

FNAB, fine-needle aspiration biopsy; TBLB, transbronchial lung biopsy.

Table 2. Results of Logistic Regression Analysis for Predictors of False-Negative Lesions on FNAB

Variable	Univariate	*p* value	Multivariate (Model 1) (n=132)	*p* value	Multivariate (Model 2) (n=222)	*p* value
Age >60 yrs	1.99 (1.16–3.42)	0.013	1.52 (0.657–3.54)	0.327	1.75 (0.985–3.12)	0.057
SUVmax (>6.7)	4.13 (1.73–9.88)	0.001	4.46 (1.79–11.1)	0.002	N/A	N/A
MTV2.5 (>2.25 mL)	2.56 (1.22–5.4)	0.013	N/A	N/A	N/A	N/A
TLG2.5 (>6.6)	2.59 (1.23–5.45)	0.013	N/A	N/A	N/A	N/A
Size of lesion (>13.5 mm)	3.04 (1.46–6.36)	0.003	1.61 (0.549–4.7)	0.387	2.51 (1.16–5.43)	0.02
Lesion characteristics (subsolid nodule)	5.6 (1.58–19.8)	0.008	11.2 (1.36–92)	0.025	5.61 (1.55–20.3)	0.009
Area under the curve of ROC curve	N/A	N/A	0.738	N/A	0.658	0.069 (Model 1 vs. Model 2)

FNAB, fine-needle aspiration biopsy; N/A, non-applicable; SUVmax, maximum standardized uptake value; MTV, mean tumor volume; TLG, total lesion glycolysis; ROC, receiver operating characteristic.
Data are presented as odds ratio (95% confidence interval).

Table 4. Clinical Characteristics of False-Negative Lesions with Upgrade in Staging

	Age/gender	Serum tumor marker	Lesion size (mm)	Lesion type	SUVmax	FNAB result	Final pathology	Method of confirmation	Tentative staging at FNAB	Staging at final diagnosis	Interval between FNAB and final diagnosis (days)
1	74/female	N/A	14.8	Solid	N/A	Negative for malignancy	Adenocarcinoma	Surgery	1a	4	590
2	78/male	Not elevated	29.6	Solid	10.5	Negative for malignancy	Unknown	Follow up	1b	3b	288
3	72/male	Not elevated	11.6	Solid	N/A	Negative for malignancy	Small cell lung cancer	Bronchoscopic biopsy	Limited	Extensive	217
4	68/female	Not elevated	40.2	Solid	12.9	Negative for malignancy	NSCLC	FNAB	3a	4	128
5	66/male	Not elevated	26	Solid	N/A	Negative for malignancy	NSCLC	Surgery for brain metastasis	3a	4	164

SUVmax, maximum standardized uptake value; FNAB, fine-needle aspiration biopsy; N/A, non-applicable; NSCLC, non-small cell lung cancer.

0.988 (95% CI, 0.964–1.0) for presence of necrosis, and 1.0 (95% CI, 1.0) for presence of cavitation.

Factors predicting false-negative lesions on FNAB cytology

Age >60 years, lesion size >13.5 mm, SUVmax >6.7, MTV >2.25 mL, and TLG >6.6 were used as best cutoff values for logistic regression analysis. Univariate logistic regression analysis showed that age, increased FDG uptake on PET (SUVmax, MTV, and TLG), lesion size, and subsolid lesion characteristics were significant predictors of false-negative lesions. Among the PET parameters, we used only SUVmax for multivariate logistic regression analysis to predict false-negative results, because the PET parameters showed multicollinearity in multivariable analysis and the SUVmax showed the highest OR on univariate analysis. On multivariate logistic regression analysis, Model 1 showed that SUVmax and lesion characteristics of subsolid lesion were significant, independent predictors of false-negative results (Table 2). Lesion characteristic and lesion size were significant independent predictors in Model 2.

Clinical outcomes of false-negative lesions

The final pathologic results, the method of confirmation of final diagnosis, and the interval between FNAB and final diagnosis for false-negative lesions are shown in Table 3. Among 90 lesions confirmed as primary lung cancer, five cases (5.6%) showed an upgrade in staging at the time of final diagnosis, compared with the tentative stage at the time of FNAB (Table 4).

DISCUSSION

This study demonstrated that increased FDG uptake on PET, large lesion size, and subsolid lesion characteristics are independent predictors of false-negative pulmonary lesions after obtaining nonspecific benign cytologic results from percutaneous transthoracic FNAB. After evaluation of multiple clinical, radiologic, and procedure-related factors, SUVmax >6.7, lesion size over 13.5 mm, and subsolid lesion characteristics were revealed to be significant predictors of false-negative results in different models of multivariate logistic regression analysis. Age over 60 years was a significant predictor on univariate analysis, but not on multivariate logistic regression analysis.

In clinical practice, early diagnosis of lung malignancy is important for proper management of the patients. Although transthoracic FNAB has been suggested as a nonsurgical technique for obtaining histopathologic diagnosis from suspicious pulmonary lesions, the major limitation of this procedure is its relatively low diagnostic yield for specific benign lesions with variable false-negative rates in the diagnosis of pulmonary nodules or masses. Therefore, patients with suspected lung malignancy and nonspecific benign cytologic results on initial FNAB often require a second biopsy such as surgical biopsy.

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Several studies have investigated the false-negative rates of FNAB and factors related to false-negative results.[6,8] These studies suggested a few factors predictive of false-negative results, for example large lesion size and occurrence of pneumothorax. In our study, large lesion size was a significant predictor on logistic regression analysis, but the other factors were not significant. Large lesion size may increase false-negative rates because the portion of the lesion with malignant cells is probably part of a larger consolidation, making it difficult to distinguish the primary lesion from surrounding atelectasis or inflammation.[6] Occurrence of pneumothorax has been reported to limit the ability to put the needle tip in the lesion and also the number of passes, which can lead to a decrease in diagnostic yield of percutaneous transthoracic FNAB.[6,14] However, the occurrence of procedure-related complications including pneumothorax was not significantly different between true-negative and false-negative lesions in our study. Our study also demonstrated that higher FDG uptake and subsolid lesion characteristics were all significant predictors for false-negative lesions. In addition to the well-known utility of PET for diagnosis, staging, and prediction of prognosis in lung cancer,[15,16] we suggest that PET can be used for the prediction of false-negative lesions on FNAB.

Subsolid lesions are known to have lower diagnostic accuracy on FNAB than solid pulmonary nodules due to their low cellularity, particularly in pure ground-glass nodules.[17] Additionally, on pathologic examination, the probability of interpretation error may be high for adenocarcinomas, which are usually pathologic determinants of subsolid lesions present on CT. A recent study regarding false-negative results from FNAB specimens reported that most interpretation errors in false-negative cases (8 of 11, 72.7%) were confirmed as adenocarcinoma.[18] They suggested that a diagnosis of adenocarcinoma can sometimes be difficult to confirm, particularly when necrosis is abundant. In our study, 54 of 115 false-negative cases (47.0%) were confirmed as adenocarcinoma (52 primary and two metastatic adenocarcinomas) on final analysis.

Numerous studies have documented close correlations between CT and pathologic findings in patients with lesions in the spectrum of adenocarcinomas of the lung. Subsolid nodules on CT may represent atypical adenomatous hyperplasia (AAH), adenocarcinoma *in situ*, minimally invasive adenocarcinoma, or lepidic predominant invasive adenocarcinoma.[19-21] Small persistent pure ground-glass nodules, particularly those smaller than 5 mm, often represent foci of AAH; in contrast, the larger the solid component of a lesion, the worse the prognosis.[22-29] Therefore, solitary subsolid nodules or dominant nodules among multiple subsolid nodules (solid component >5 mm) should be considered malignant and be recommended for transthoracic biopsy or surgical excision.[30] Considering the low diagnostic yield of transthoracic FNAB for subsolid nodules, transthoracic core needle biopsy or surgical excision would be better methods for tissue confirmation.

Previous studies have reported a wide range of false-negative rates of percutaneous transthoracic FNAB.[6-8,10,31,32] The false-negative rate (51.8%) of our study is within the range of previous results, but is relatively high. Possible reasons for this high false-negative rate, compared with other studies, are different inclusion criteria, such as a relatively long follow-up period of over 2 years, different definition of negative lesions, the absence of an on-site cytologist, and exclusion of lesions with core biopsy. We excluded lesions without cytopathologic confirmation or at least 2 years of imaging follow up, as such lesions may have a high probability of being benign. Studies on the diagnostic performance of percutaneous transthoracic FNAB vary regarding the definition of 'negative lesions.' Some studies included cases with inadequate specimen or specific benign results in the negative category. This variation in definition may result in a wide range of reported false-negative rates. In our study, lesions with inadequate specimens were not included because such lesions have been reported to show a higher false-negative rate than lesions with nonspecific benign results, mostly because of the higher possibility of sampling error with an inadequate specimen.[8,10] A number of studies have reported the value of having a cytologist present at the time of a biopsy procedure to reduce the number of biopsy specimens required to achieve a diagnosis.[33-35] Although many institutions have on-site cytologists, the lack of one in our study might lead to an increased risk of sampling errors, thus the aspirated specimen might not accurately represent the lesion characteristics. However, this is not possible in many centers, including our institution. Because an on-site cytologist was not available, we included only lesions with nonspecific benign results. Many studies reported the diagnostic value of core needle biopsy in transthoracic biopsy, in terms of higher diagnostic accuracy than FNAB alone, by reducing sampling error due to obtaining large amounts of sample.[36-39] However, we did not include lesions that were biopsied with core needle, because only a small number of referred pulmonary lesions (119 of 1829 lesions, 6.5%) underwent core needle biopsy for varying reasons, such as high risk of procedure-related complications or preference of biopsy-performing radiologists or referring clinicians.

Our study has several limitations. First, because of the retrospective nature of the study, some degree of selection bias was present and a relatively high false-negative rate was obtained. Many lesions lacking an adequate follow-up period were excluded and most of these had a high probability of being benign. Nonetheless, the false-negative rate (51.8%) of our study was within the range of previous results. Second, as rapid on site evaluation of cytopathology was not available in the FNAB room, we excluded lesions with inadequate specimen from the analysis to reduce the impact of sampling error. Third, PET parameters were significant predictors for false-negative results; however, these quantitative parameters were not available in all patients. Therefore, we constructed two models of multivariate logistic regression analysis. Fourth, because only

a small number of false-negative lesions (5 cases) showed an upgrade in staging at the time of final diagnosis, the impact of delayed diagnosis on prognosis in cases with false-negative results on FNAB could not be determined. However, all five cases were terminal stage (stage 3b or 4 in non-small cell cancer and extended stage for small cell lung cancer) at the time of final diagnosis. Therefore, delayed diagnosis may be critical for patient management and prognosis.

In conclusion, despite the common use of FNAB, there are appreciable numbers of false-negative results after the initial FNAB. Among the clinical, radiologic, and procedure-related factors analyzed, high FDG uptake, large lesion size, and subsolid lesion were useful factors for predicting malignancy in pulmonary lesions with nonspecific benign cytology results on FNAB. Therefore, lesions with these characteristics should be more carefully followed up or considered for re-biopsy.

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